32. (Twice amended) A neutralizing monoclonal antibody having a [high titer] dissociation constant equal to or less than about 2×10^{-10} M for human interleukin-4, a Fab fragment or a $F(ab')_2$ fragment thereof, produced by screening a library of hydridoma products with aldehyde labeled human interleukin-4 or biotinylated human interleukin-4.

REMARKS

Claims 1-11, 14-18 and 30 - 39 are pending in the application. Claims 1, 5, 16, 30 and 32 have been amended. Claim 40 has been canceled without prejudice. No new matter has been added.

Moreover, the Applicant reserves the right to prosecute, in one or more patent applications, the canceled claims, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. Any amendments made to the claims herein were made to solely expedite and facilitate prosecution and were not made nor should they be construed to have been made to overcome any issue of unpatentability of the claims prior to amendment or in acquiescence of the Examiner's rejections to the claims.

Applicants note that an Information Disclosure statement was filed in the above-identified application on February 27, 1998. Consideration and acknowledgment of the references cited therein is respectfully requested.

Provisional Double Patenting Rejection

Claims 1 - 11, 14 - 17, 30 and 32 - 38 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 - 11, 14 - 17, 30 and 32 - 38 of co-pending Application Serial No. 08/483,636. As acknowledged by the Examiner, Applicants submit that, prior to patent issuance, any outstanding double patenting issues remaining in the applications will be resolved.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1 - 4 and 17 - 18 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which is not enabled by the specification. These rejections are respectfully traversed.

It is submitted that one of skill in the art, based on the the teachings in the specification and the knowledge of one of skill in the art, would be able to make and use the claimed invention as written. However, solely to expedite prosecution, Applicants have amended claim 1 to recite that the heavy and light chain CDRs are operatively positioned within the first fusion partner, which is defined in the specification on pages 5 – 6 as follows:

> a nucleic acid sequence encoding a human framework or human immunoglobulin variable region in which the native (or naturally occuring) CDRs are replaced by the CDRs of a donor antibody. The human variable region can be an immunoglobulin heavy chain, a light chain (or both chains), an analog or functional fragments thereof. Such CDRs or CDR regions, located within the variable region of antibodies (immunoglobulins) can be determined by known methods in the art. For example Kabat et al., [Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institues of Health (1987)], disclose rules for locating CDRs. In addition, computer programs are known which are useful for identifying CDR regions/structures.

As such it is submitted that the claims are fully enabled by the specification and therefore, it is respectfully requested that the rejections under 35 U.S.C. 112 be withdrawn.

Further, it is submitted that the specification provides a detailed description of the selection and insertion of the appropriate CDR sequence and that one of skill in the art would be able to use one or more isolated CDRs in the appropriate positions. Additionally, it is submitted that the specification, *inter alia* on pages 15 - 17, clearly describes the selection of appropriate framework regions.

Moreover, the Examiner, in the previous Office Action, asserts that "all of the heavy and light chain CDRs in their proper order and fused to appropriate human framework sequences are required in order to produce a protein having antigen-binding function". However, the Examiner has provided no basis to support this assertion. Applicants submit, as shown in the enclosed abstracts, that isolated CDR peptides can retain the binding specificity of the parent mAb.

In light of the above arguments, it is respectfully requested that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

35 U.S.C. § 102

Claim 30 was rejected under 35 U.S.C. § 102(b) as being anticipated by JP-327725. This rejection is respectfully traversed in that JP-327725 is limited to a method of determining the level of IL-4 in a sample and fails to teach or suggest a diagnostic method or that such a method is useful for identifying patients with conditions associated with excess IgE production. As such, it is respectfully requested that this rejection be withdrawn.

35 U.S.C. § 102/103

Claim 32 was rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as being obvious over Ramanathan et al. or JP-327725 or Chretien et al. These rejections are respectfully traversed for the reasons set forth below.

Among the features of the present invention which Ramanathan et al. or JP 327725 or Chretien et al. fail to disclose or suggest are a neutralizing antibody or an antibody with a dissociation constant equal to or less than 2×10^{-10}. The Examiner has asserted that there is no dissociation constant mentioned in claim 32. Applicants respectfully note that claim 32 recites a "neutralizing monoclonal antibody having a high titer for human interleukin 4 ..." (emphasis added). As defined in the specification on page 6, lines 10 – 11, "[t]he term "high titer" refers to an antibody having a binding affinity characterized by a K_d equal to or less than 2×10^{-10} M for human IL4". As such, it is submitted that the cited references fail to teach or suggest a monoclonal antibody which is specific for human IL-4 and has a "high titer". However, solely to expedite prosecution, claim 32 has been amended.

As to the Examiner's citation to Harlow and Lane, Applicants submit that this reference fails to remedy the deficiencies of the primary references. In particular, Harlow et al. is a general text directed to antibodies and, in the cited portion, provides a general range of affinity constants for monoclonal antibodies. However, this reference fails to teach or suggest how to make or identify antibodies with a dissociation constant equal to or less than 2×10^{-10} M or teach or suggest antibodies with such characteristics which are specific for human IL-4. As such, it is respectfully requested that the rejections under 35 U.S.C 102 or 103 be withdrawn.

35 U.S.C. § 103

Claim 1 was rejected under 35 U.S.C. 103(a) as being obvious over Ramanathan et al. or JP-327725 or Chretien et al. Claims 1 - 2, 4, 14 - 17, 30 - 34 and 36 were rejected under 35 U.S.C. § 103 as being unpatentable over Queen et al. in view of Abrams et al., Chretien et al. and Curtis et al. These rejections are respectfully traversed for the reasons set forth below.

It is submitted that the references cited by the Examiner, no matter how combined, do not teach or suggest the present invention. In particular, as discussed above, the cited references fail to teach or suggest a high affinity, neutralizing IL4 antagonist, as claimed.

The Queen reference fails to remedy the deficiencies of the other references cited by the Examiner. This reference is limited to general techniques and does not suggest the aspects of the claims which make the constructs patentable. Particularly, this reference fails to disclose or suggest high affinity, neutralizing IL4 antagonists or the portion of the claimed antibodies which contribute to the high affinity thereof.

Further, as discussed above, as to the Examiner's citation to Harlow and Lane, Applicants submit that this reference fails to remedy the deficiencies of the primary references. In particular, Harlow et al. is a general text directed to antibodies and, in the cited portion, provides a general range of affinity constants for monoclonal antibodies. However, this reference fails to teach or suggest how to make or identify antibodies with a dissociation constant equal to or less than 2×10^{-10} M or teach or suggest antibodies with such characteristics which are specific for human IL-4. As such, it is respectfully requested that the rejections under 35 U.S.C 102 or 103 be withdrawn.

Claim 31 was rejected under § 103 as allegedly being unpatentable over WO 91/09059 or Chretien et al. This rejection is respectfully traversed for the reasons set forth below.

Since the Examiner appears to have overlooked the arguments provided for this rejection, the Applicants repeat those arguments herein.

As to the rejection of claim 31 over WO 91/09059 or Chretien et al., this rejection is respectfully traversed in that these references fail to teach or suggest a method of screening for monoclonal antibodies which have high titer for human IL-4 wherein the human IL-4 is not denatured during the screening, as is claimed. As such, it is respectfully requested that this rejection be withdrawn.

New Grounds of Rejection

35 U.S.C. § 103

Claims 1 and 40 were rejected under 35 U.S.C § 103 as being obvious over Loh et al. This rejection is respectfully traversed for the reasons set forth below.

As to claim 1, it is submitted that Loh et al. fail to teach or suggest a fusion protein which has binding specificity for human interleukin-4, as is claimed. Loh et al. is limited to a disclosure of the CDRs of myeloma antibodies. As such, it is respectfully requested that the rejection of claim 1 be withdrawn. As to claim 40, it is submitted that this rejection is moot in light of the cancellation of claim 40.

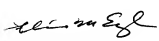
Provisional Obviousness-type Double Patenting Rejection

Claims 1 and 39 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 10 of co-pending Application Serial No. 08/483,636. As noted above, Applicants submit that, prior to patent issuance, any remaining double patenting issues will be addressed.

In light of the above arguments and amendments, it is submitted that all of the claims are in condition for full and complete allowance and therefore, such action is respectfully requested.

If there are any amendments or issues the Examiner wishes to discuss, she is encouraged to contact the undersigned by telephone.

Respectfully submitted,



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